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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,438	11/14/2001	Avi J. Ashkenazi	10466/201	2374

35489 7590 04/20/2004

HELLER EHRMAN WHITE & MCAULIFFE LLP  
275 MIDDLEFIELD ROAD  
MENLO PARK, CO 94025-3506

EXAMINER

KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/990,438	<b>Applicant(s)</b> ASHKENAZI ET AL.	
	<b>Examiner</b> Claire M. Kaufman	<b>Art Unit</b> 1646	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 16 November 2002.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 119-131 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 119-131 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>05/28/02</u> . | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

The preliminary amendments filed 11/14/01 and 9/03/02 have been entered.

#### *Specification*

5           The disclosure is objected to because of the following informalities: on p. 548, line 19, “samples” should be “sample”.

Appropriate correction is required.

#### *Claim Rejections - 35 USC § 112, Second Paragraph*

10           The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15           Claims 119-124, 127, 128, and dependent claims 125, 126 and 129-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20           Claims 119-124, 127, 128 are indefinite for reciting “extracellular domain”. The protein identified as PRO290 is disclosed as an intracellular protein (p. 340, line 20). It is not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed protein comprises an “extracellular domain” (for example see claim 119, parts (c) and (d)) is indefinite, as the art does not recognize intracellular proteins as having such a domain. Further, if the protein had an extracellular domain, the recitation of “the extracellular domain...” lacking its associated signal sequence” (claim 39, part (d), for example) is indefinite because a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences  
25           are cleaved from said domains in the process of secretion from the cell.

#### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

30           Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

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Claims 119-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are drawn to a polypeptide. While the disclosed nucleic acid of SEQ ID NO:33, which encodes the protein called PRO290, has utility as a screening probe to detect squama cell-type lung carcinomas (pages 550, TABLE 9A), the polypeptide has not such utility. There is no specific or substantial function attributable to the polypeptide, and even though it is stated that PRO290 is most related to FAN and beige proteins (p. 410, line 18), a shared identity of less than 20% is too low to reliably extrapolate function from structure (see SEQUENCE COMPARISON US 5,952,223). Further, the function of these proteins was unclear in the prior art. The prior art does not provide sufficient information to allow the skilled artisan to use PRO290 without significant further research.

Even though the nucleic acid has utility as a probe for screening for lung tumor cells, the encoded polypeptide has no such utility since there is no reason to suspect that there is alteration of polypeptide sequence or amount in lung tumor *versus* normal tissue. Even if the DNA has utility as a lung tumor marker, the encoded protein does not have utility because it is not known what the protein does or if the level of PRO290 protein in lung tumors corresponds to nucleic acid transcript level, *i.e.*, if an increased gene amplification in lung tumors corresponds to an increased amount of expressed protein. It does not necessary follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the polypeptide would be useful diagnostically or as a target for cancer drug development. For example, Pennica et al. (1998, PNAS USA 95, p.14722, second paragraph) teach that:

An analysis of WISP-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient.

Additionally, Hayes et al. (Electrophoresis 19 :1862-1871, 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and

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Figure 1). Therefore, because it cannot be concluded that PRO290 is associated with formation or growth of lung tumor or is useful itself as a diagnostic marker for lung cancer, the encoded protein does not have utility. Significant further research would be required to find out what the protein does and if and how it is linked to lung cancer.

5 For these reasons, there is no substantial and specific utility for the claimed polypeptide.

***Claim Rejections - 35 USC § 112, First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

10 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15 Claims 119-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

20 The specification provides little beyond structural data and potential activities of the PRO290 polypeptide without guidance about which specific activities one could reasonably expect the polypeptide to possess as discussed above. Also, the claims have great breadth allowing for 80% identity to a partial sequence. Therefore, it would require undue experimentation to use the claimed invention. For these reasons which include breadth of the claims, lack of information on the relationship of structure to function of PRO290, paucity of information in the prior art, limited working example, and lack of guidance for use provided in  
25 the specification, it would require undue experimentation to use the claimed nucleic acid commensurate in scope with the claims.

30 Claims 119-124, 126, 128 and 132-138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

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skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims lack written description on two counts. First, claims are drawn to, for example, a polypeptide of SEQ ID NO:33 lacking its associated signal sequence. It is not clear if PRO290 has a signal sequence or if it does, what that sequence is. The specification discloses PRO290 of SEQ ID NO:33, but no domains are disclosed. The specification says PRO290 is believed to be an intracellular protein (p. 349, line 20). While there is some relationship to intracellular proteins FAN and beige (p. 410, line 18), shared sequence identity is not high (less than 20%, see SEQUENCE COMPARISON US 5,952,223) so correspondence to structure is difficult to make. It does not appear Applicants were in possession of a polypeptide specifically lacking (or specifically including) a signal sequence.

Second, the claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Which polypeptides of the genus comprising the required sequence are part of the invention has not been set forth.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of

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ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116).

As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only a polypeptide of SEQ ID NO:33, but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

### ***Priority***

Priority application 09/380,137 and earlier filed priority applications do *not* meet the requirements of 35 U.S.C. § 112, first paragraph. While the sequence of PRO290 is disclosed, there was no function/use known to be associated with PRO290, and the skilled artisan would not have known how to use it. Therefore, the prior application also does not meet those requirements and, therefore, is unavailable under 35 U.S.C. § 120. Note that even if priority were granted to the earliest filed priority application 60/092,472, the art rejection would remain under 35 UCS 102(a).

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 119-123, 126, 128 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank AB011112.1.

GenBank AB011112.1 teaches a nucleic acid encoding a protein at least 99% identical to SEQ ID NO:33 of the instant application. See attached SEQUENCE COMPARISON GenBank  
5 AB011112.1.

### *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571)272-0873.

10 Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571)272-0871.

Any inquiry of a general nature or relating to the status of this application should be  
15 directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 872-9306. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to  
20 avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.



Patent Examiner, Art Unit 1646

25 April 15, 2004



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**SEQUENCE COMPARISON GenBank AB011112****Part of 09/990,438 page 8**

AC 060288;  
 DT 01-AUG-1998 (TrEMBLrel. 07, Created)  
 DT 01-OCT-2002 (TrEMBLrel. 22, Last sequence update)  
 DT 01-MAR-2003 (TrEMBLrel. 23, Last annotation update)  
 DE KIAA0540 protein (Fragment).  
 GN KIAA0540.  
 OS Homo sapiens (Human).  
 OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;  
 OC Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.  
 OX NCBI\_TaxID=9606;  
 RN [1]  
 RP SEQUENCE FROM N.A.  
 RC TISSUE=Brain;  
 RX MEDLINE=98290545; PubMed=9628581;  
 RA Nagase T., Ishikawa K., Miyajima N., Tanaka A., Kotani H., Nomura N.,  
 RA Ohara O.;  
 RT "Prediction of the coding sequences of unidentified human genes. IX.  
 RT The complete sequences of 100 new cDNA clones from brain which can  
 RT code for large proteins in vitro.";  
 RL DNA Res. 5:31-39(1998).  
 DR EMBL; AB011112; BAA25466.3; -  
 DR InterPro; IPR000409; Beige\_BEACH.  
 DR InterPro; IPR001680; WD40.  
 DR Pfam; PF02138; Beach; 1.  
 DR Pfam; PF00400; WD40; 2.  
 DR ProDom; PD007848; Beige\_BEACH; 1.  
 DR SMART; SM00320; WD40; 3.  
 DR PROSITE; PS50197; BEACH; 1.  
 DR PROSITE; PS50082; WD\_REPEATS\_2; 2.  
 DR PROSITE; PS50294; WD\_REPEATS\_REGION; 1.  
 KW Repeat; WD repeat.  
 FT NON\_TER 1 1  
 SQ SEQUENCE 2041 AA; 224474 MW; CC523F1D5D041F51 C RC64;

Query Match 99.5%; Score 5222; DB 4; Length 2041;  
 Best Local Similarity 97.1%; Pred. No. 0;  
 Matches 1003; Conservative 0; Mismatches 0; Indels 30; Gaps 1;

QY 1 MSQFEMDTYAKSHDLMSGFWNACYDMLMSSGQRRQWERAQSRRAFQELVLEPAQRRARLE 60  
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||  
 Db 1009 MSQFEMDTYAKSHDLMSGFWNACYDMLMSSGQRRQWERAQSRRAFQELVLEPAQRRARLE 1068  
 QY 61 GLRYTAVLKQQATQHSMALLHWGALWRQLASPCGAWALRDTPIPRWKLSSAETYSRMRLK 120  
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||  
 Db 1069 GLRYTAVLKQQATQHSMALLHWGALWRQLASPCGAWALRDTPIPRWKLSSAETYSRMRLK 1128  
 QY 121 LVPNHFFDPHLEASALRDNLGEVPLTPTEEASLPLAVTKEAKVSTPPELLQEDQLGEDEL 180  
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||  
 Db 1129 LVPNHFFDPHLEASALRDNLGEVPLTPTEEASLPLAVTKEAKVSTPPELLQEDQLGEDEL 1188  
 QY 181 AELETPMEEAELDEQREKLVLSAECQLVTVVAVVPGLLEVTTQNVYFYDGSTERVETEEG 240  
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||  
 Db 1189 AELETPMEEAELDEQREKLVLSAECQLVTVVAVVPGLLEVTTQNVYFYDGSTERVETEEG 1248

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Qy	241	IGYDFRRPLAQLREVHLRRFNLRRSALELFFIDQANYFLNFPCKVGTTPVSSPSQTPRPQ	300
Db	1249	IGYDFRRPLAQLREVHLRRFNLRRSALELFFIDQANYFLNFPCKVGTTPVSSPSQTPRPQ	1308
Qy	301	PGPIPPHTQVRNQVYSWLLRLRPPSQGYLSSRSPQEMLRASGLTQKWVQREISNFEYLMQ	360
Db	1309	PGPIPPHTQVRNQVYSWLLRLRPPSQGYLSSRSPQEMLRASGLTQKWVQREISNFEYLMQ	1368
Qy	361	LNTIAGRITYNDLSQYPVFPWVLQDYVSPTLDLSNPAVFRDLSKPIGVVNPKHAQLVREKY	420
Db	1369	LNTIAGRITYNDLSQYPVFPWVLQDYVSPTLDLSNPAVFRDLSKPIGVVNPKHAQLVREKY	1428
Qy	421	ESFEDPAGTIDKFHYGTHYSNAAGVMHYLIRVEPFTSLHVQLQSGRFDSCDRQFHSVAAA	480
Db	1429	ESFEDPAGTIDKFHYGTHYSNAAGVMHYLIRVEPFTSLHVQLQSGRFDSCDRQFHSVAAA	1488
Qy	481	WQARLESPADVKELIPEFFYFPDFLENQNGFDLGCLQLTNEKVGDDVLPWPASSPEDFIQ	540
Db	1489	WQARLESPADVKELIPEFFYFPDFLENQNGFDLGCLQLTNEKVGDDVLPWPASSPEDFIQ	1548
Qy	541	QHRQALESEYVSAHLHEWIDLIFGYKQRGPAABEALNVFYCYTYEGAVDLDHVTDERERK	600
Db	1549	QHRQALESEYVSAHLHEWIDLIFGYKQRGPAABEALNVFYCYTYEGAVDLDHVTDERERK	1608
Qy	601	ALEGIISNFGQTPCQLLKPEHPTRLASAEAAHRLARLDTNSPSIFQHLDELKAFFAE---	657
Db	1609	ALEGIISNFGQTPCQLLKPEHPTRLASAEAAHRLARLDTNSPSIFQHLDELKAFFAEVVS	1668
Qy	658	-----VTVSASGLLGTHSWLPYDRNISNYFSFSKDPTM	690
Db	1669	DGVPLVLALVPHRQPHSFITQGSDDLVTVSASGLLGTHSWLPYDRNISNYFSFSKDPTM	1728
Qy	691	GSHKTQRLLSGPWPVPGSGVSGQALAVAPDGKLLFS GGHWDGSLRVLTALPRGKLLSQLSCH	750
Db	1729	GSHKTQRLLSGPWPVPGSGVSGQALAVAPDGKLLFSGGHWDGSLRVLTALPRGKLLSQLSCH	1788
Qy	751	LDVVTCLALDTCGIYILISGSRD TTCMVWRL LHQGLSVGLAPKPVQVLYGHGAAVSCVAI	810
Db	1789	LDVVTCLALDTCGIYILISGSRD TTCMVWRL LHQGLSVGLAPKPVQVLYGHGAAVSCVAI	1848
Qy	811	STELDMAVSGSEDGTVI IHTVRRGQFVAALRPLGATFPGPI FHLALGSEGGIVVQSSAW	870
Db	1849	STELDMAVSGSEDGTVI IHTVRRGQFVAALRPLGATFPGPI FHLALGSEGGIVVQSSAW	1908
Qy	871	RPGAQVITYSLHLYSVNGKLRASLPLAEQPTALTVTEDFVLLGTAQCALHILQLNTLLPAA	930
Db	1909	RPGAQVITYSLHLYSVNGKLRASLPLAEQPTALTVTEDFVLLGTAQCALHILQLNTLLPAA	1968
Qy	931	PPLPMKVAIRSAVATKERSHVLVGLEDGKLI VVVAGQPSEVRSSQFARKLWRSSRRISQV	990
Db	1969	PPLPMKVAIRSAVATKERSHVLVGLEDGKLI VVVAGQPSEVRSSQFARKLWRSSRRISQV	2028
Qy	991	SSGETEYNPTPEAR	1003
Db	2029	SSGETEYNPTPEAR	2041

SEQUENCE COMPARISON US 5,952,223 Part of 09/990,438 page 10

; Patent No. 5952223  
; GENERAL INFORMATION:  
; APPLICANT: Kaplan, Jerry  
; APPLICANT: Perou, Charles  
; APPLICANT: Moore, Karen  
; TITLE OF INVENTION: COMPOSITIONS FOR THE DIAGNOSIS  
; TITLE OF INVENTION: AND TREATMENT OF CHEDIAK-HIGASHI SYNDROME  
; NUMBER OF SEQUENCES: 32  
; CURRENT APPLICATION DATA:  
; APPLICATION NUMBER: US/08/822,445  
; FILING DATE: 21-MAR-1997  
; INFORMATION FOR SEQ ID NO: 2:  
; SEQUENCE CHARACTERISTICS:  
; LENGTH: 2186 amino acids  
; TYPE: amino acid  
; TOPOLOGY: unknown  
; MOLECULE TYPE: protein  
; FRAGMENT TYPE: internal  
US-08-822-445-2

Query Match 16.8%; Score 882; DB 2; Length 2186;  
Best Local Similarity 27.9%; Pred. No. 1.2e-70;  
Matches 295; Conservative 147; Mismatches 338; Indels 276; Gaps 43;

Qy 5 EMDTYAKSHDLMMSGFWNACYDMLMSSGQRRQWERAQSR-RAFQELVLEPAQRRARLEGLR 63  
| | : | | : : | : : : : | : : :  
Db 1231 EQKKEYEESVSKGSW----QKTVMNNQQLFQRLDFKSKDISKIAADITQAVSLSQGIE 1286  
Qy 64 YTAVLKQQATQHSM---ALLHWGALWRQLASPCGAWALRDTPI---PRWKLSSAETYSRM 117  
| : : : | | : | | | | : | : |  
Db 1287 RKKVIQHIRGMYKVDLSASRHWQECIQQLTHDRAVWY---DPIYYPTSWQLDPTEGPNRE 1343  
Qy 118 RLKL-----VPNHHFDPHLEASALRD-NLGEVPLTPTEEASLPLAVTKEAKVSTPPELL 170  
| : | : | : | | | | | : | : |  
Db 1344 RRRLQRCYLTI PNKYL-----LRDRQKSEGVLRP-----PLSYLFEDKTHSSFSST 1389  
Qy 171 QEDQLGEDELALETPMEAAELDEQREKLVLSAECQLVTVVAVVPGLLEVTTQNVYFY-D 229  
: | : : : | | : | : | : | : | :  
Db 1390 VKDKAASESIRVNRRCISVAPSRETAGELL-LGKC-----GMYFVED 1430  
Qy 230 GSTERVETEEGIG----YDFRRPLAQLREVHLRRFNLRRSALELFFIDQANYFLNFPCKV 285  
: : | : | : : | : : | : | : : : : :  
Db 1431 NASDAVESSSLQGELEPASFSWTYEEIKEVHRRWWQLRDNAVEIFLTNGRTLALLAF---- 1486  
Qy 286 GTTPVSSPSQTPRPQPGPIPPHTQVRNQVYSWLLRLRPPSQGYLSSRSPQ--EMLRASGL 343  
: : | : | | | : | : | : | : | : |  
Db 1487 -----DNNKVRDDVY-----QSILTNLNLPLEYGNITAL 1516  
Qy 344 TQKWVQREISNFEYLMQLNTIAGRTYNDLSQYPVFPWVLQDYVSPTLDLSNPAVFRDLSK 403  
| | : | : | | | | : | : | | | : | : | : | : | : | : | : | :  
Db 1517 TNLWYSGQITNFEYLTNLKHAGRSFNDLMQYPVFPFILSDYVSETLDLNDPSIYRNLSK 1576  
Qy 404 PIGVVPKHAQLVREKYESFE-----DPAGTIDKFHYGTHYSNAAGVMHYLIRVE 453  
| | | : : | : | | : : | : | : | : | : | : | : | :  
Db 1577 PIAVQYKEKEDRYVDTYKYLEEEYRKGAREDDMPMPVQPYHYGSHYSNSGTVLHFLVRMP 1636

Qy 454 PFTSLHVQLQSGRFDSCDRQFHSVAAAWQ-ARLESPADVKELIPEFFYFPDFLENQNGFD 512  
 ||| : : | || || ||| : : || ||||| ||| : || : |||  
 Db 1637 PFTKMFAYQDQSFIDPDRTFHSTNTTWRLLSSFESMTDVKELIPEFFYLPEFLVNREGFD 1696

Qy 513 LGCLQLTNEKVGDVVLPPWA-SSPEDFIQQHRQALESEYVSAHLHEWIDLIFGYKQRGPA 571  
 | | : | | |||| : | || ||||| : || : ||| : |||| : | |  
 Db 1697 FGVRQ-NGERVNVHVNLPWARNDPRLFILHRQALESDHVSQNICHWIDLIVFGYKQKGKA 1755

Qy 572 AEEALNVFYCYTYEGAVDLHDVTDERERKALEGII SNFGQTPCQLLKEPHPTRLSAE--- 628  
 : : ||| : || | : : | | : : ||| : | : ||| || | : | | :  
 Db 1756 SVQAINVFHPATYFG-MDVSAVEDPVQRRALETMIKTYGQTPRQLFHTAHASRPGAKLNI 1814

Qy 629 -----EAAHRLAR---LDTNSPSIFQHLDELKAFFAEVTVSASG----- 664  
 : | | | : || : || : | | |  
 Db 1815 EGELPAAVGLLVQFAFRETREPVKEVTHPSPLSWIKGLK--WGEYVGSPSAPVPVVCFSQ 1872

Qy 665 -----LLGTH-----SWLPYDRNIS 679  
 || | : || | ||  
 Db 1873 PHGERFGSLQALPTRAICGLSRNFCLLMTYNKEQGVRSMNNTNIQWSAILSW-GYADNIL 1931

Qy 680 NYFSFSKDPTMG---SHKTQRLLSGPWVPGSGVSGQALAVAPDGKLLFSGGH-----WD 730  
 | : | : | : : | || || ||| : :  
 Db 1932 RLKSKQSEPPINFIQSSQHQVTSCAWV-----PDSCQLFTGSKCGVITAYT 1978

Qy 731 GSLRVTALPRGKLLSQLSC--HLDVVTCLALDTCGIY--LISGSRDTCMVW---RLLHQ 783  
 | : : || : | : : | | : || ||| ||| : || :  
 Db 1979 NRLTSSTPSEIEMESQMHLYGHTTEITGLCV--CKPYSVMISVSRDGTICVWDLNRLCY- 2035

Qy 784 GGLSVGLAPKPVQVLYGHGAAVSCVA-----ISTELDMAVSGSE-----DGTVIIHT 830  
 || | || : | : : | : | | || : : | : |  
 Db 2036 -----VQSLAGHKSPVTAVSASETSGDIATVCDSAGGSDLRLWTVNGDLVGH- 2083

Qy 831 VRRGQFVAAL----RPLGATFFGPFIHIALGSEGQIVVQSSAWE-----RPG 873  
 | : : : : | | : | : | | | | : : |  
 Db 2084 VHCREIICSVAFSNQPEGVS----INVIAGGLENGIVRLWSTWDLKPVREITFPKSNKPI 2139

Qy 874 AQVTYSL---HLYSVNG-----KLRASLPL 895  
 : | : ||| : | : |||  
 Db 2140 ISLTFSCDGHLYTANSEGTVIAWCRKDQQRVKLPM 2175